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Neuroendocrine Abnormalities in Patients with Traumatic Brain Injury

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Summary: This article provides an overview of hypothalamic and pituitary alterations in brain trauma, including the incidence of hypothalamic-pituitary damage, injury mechanisms, features of the hypothalamic-pituitary defects, and major hypothalamic-pituitary disturbances in brain trauma. While hypothalamic-pituitary lesions have been commonly described at postmortem examination, only a limited number of clinical cases of traumatic hypothalamic-pituitary dysfunction have been reported, probably because head injury of sufficient severity to cause hypothalamic and pituitary damage usually leads to early death. With the improvement in rescue measures, an increasing number of severely head-injured patients with hypothalamic-pituitary dysfunction will survive to be seen by clinicians. Patterns of endocrine abnormalities following brain trauma vary depending on whether the injury site is in the hypothalamus, the anterior or posterior pituitary, or the upper or lower portion of the pituitary stalk. Injury predominantly to the hypothalamus can produce dissociated ACTH-cortisol levels with no response to insulin-induced hypoglycemia and a limited or failed metopirone test, hypothyroxinemia with a preserved thyroid-stimulating hormone response to thyrotropin-releasing hormone, low gonadotropin levels with a normal response to gonadotropin-releasing hormone, a variable growth hormone (GH) level with a paradoxical rise in GH after glucose loading, hyperprolactinemia, the syndrome of inappropriate ADH secretion (SIADH), temporary or permanent diabetes insipidus (DI), disturbed glucose metabolism, and loss of body temperature control. Severe damage to the lower pituitary stalk or anterior lobe can cause low basal levels of all anterior pituitary hormones and eliminate responses to their releasing factors. Only a few cases showed typical features of hypothalamic or pituitary dysfunction. Most severe injuries are sufficient to damage both structures and produce a mixed endocrine picture. Increased intracranial pressure, which releases vasopressin by altering normal hypothalamic anatomy, may represent a unique type of stress to neuroendocrine systems and may contribute to adrenal secretion by a mechanism that requires intact brainstem function. Endocrine function should be monitored in brain-injured patients with basilar skull fractures.

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and protracted posttraumatic amnesia, and patients with SIADH or DI should be closely monitored for other endocrine abnormalities. Key Words: Brain trauma—Head injuries—Hypothalamus—Pituitary—Hormones—Neuroendocrinology.

Major trauma provokes a neuroendocrine response characterized by stimulation of the hypothalamus and results in altered secretion of pituitary hormones and activation of the sympathoadrenal system, with changes in the secretion of adrenal, pancreatic, and thyroid hormones (52,63,75). These reactions are considered nonspecific, or independent of the site of injury (117). However, head trauma patients may present different patterns of hormonal response to trauma when compared to other trauma patients. The development of a full hormonal response to trauma involves numerous pathways and centers, including afferent neural pathways, the brainstem, the cortex, corticohypothalamic pathways, hypothalamic integrative centers, the pituitary gland, and efferent autonomic pathways (169). Head injuries may disturb any part of this complex response, depending on the severity and the location of primary and secondary injuries. It is important to recognize these unique endocrine disturbances in head trauma patients because such hormonal changes may induce metabolic aberrations that have considerable diagnostic and therapeutic implications as well as great impact on the eventual outcome (85).

Despite the clinical observation of an altered endocrine profile in head trauma patients and frequent recognition of pituitary and hypothalamic damage in post-mortem studies following head injury (25,34,38,39,97), the patterns of changes in hypothalamic and pituitary hormones are not fully understood, nor is the influence of such changes on peripheral endocrine gland functions. This article provides an overview of the hypothalamic-pituitary axis alterations in traumatic brain injury. Since most previous studies have been clinical and many of them are concerned with changes in the pituitary gland in long-term survivors of head injury, very few descriptions of hypothalamic-pituitary changes in the early post-traumatic period are available.

Hypothalamic disorders can also affect many functions not mediated by the pituitary, including a large number of autonomic nervous system functions that are involved in acute and chronic neurometabolic control and regulation of the cardiovascular, pulmonary, renal, and gastrointestinal systems. These nonpituitary functions may interact with the hypothalamic-pituitary-target organ axes at various levels (126). However, the main focus of this review is the hypothalamic responses to head trauma involving the pituitary gland.

INCIDENCE

Damage to the pituitary and hypothalamus is common in patients dying of head injury (25,34,38,39,97). Daniel and Treip (39) found that of 152 patients who died from head injury, 56 (37%) exhibited lesions in the pituitary. Ceballos (25) exam-

ined pituitary glands of 102 head trauma patients from 2,500 consecutive autopsies; damage in the pituitary, mainly hemorrhage and necrosis, was found in 88 (86.3%) cases. Kornblum and Fischer (97) examined the brains of 100 patients with fatal head injury; 62 showed one or more lesions in the pituitary gland, 42 showed hemorrhages in the posterior lobe, and 22 showed ischemic necrosis of the anterior lobe. Trauma to the hypothalamus frequently occurs in serious head injuries. In Crompton's study of 106 autopsy cases with fatal head injury, hypothalamic lesions were found in 45 (42%) cases (34). It is apparent, therefore, that hypothalamic-pituitary injury is common in head trauma.

INJURY MECHANISMS

Hypothalamic Injury

The supraoptic nucleus (SON) is the most vulnerable area of the hypothalamus because of its location in relation to the optic nerve (48,95) (Fig. 1). The optic nerve is tethered rostrally at the optic foramen by the dural sheath. Caudally, it forms an angle with the lamina terminalis close to the SON. As one side of the angle is fixed, sudden movements of the brain can readily result in tearing or compression of the SON. The adjacent blood vessels may also be damaged, causing hemorrhage. Smaller lesions have been found in the paraventricular nucleus (PVN), but direct tears have not been seen, probably because it is farther away from the optic foramen (153). Subependymal hemorrhages around the third ventricle are common, and may impinge upon the PVN.

Pituitary Injury

Infarction is the major lesion in the anterior lobe of the pituitary after brain trauma. The blood supply of the anterior pituitary lobe is obtained almost exclusively from the hypophyseal portal vein system, which has both long and short portal veins (36) (Fig. 1). The long portal veins are derived from the two superior hypophyseal arteries through the plexus in the median basal eminence and the upper stalk and supply 90% of the anterior lobe of the pituitary. The short portal veins originate from the two inferior hypophyseal arteries via a capillary plexus in the lower stalk below the diaphragma sellae and only supply a few adenohypophyseal cells adjacent to the posterior pituitary. Additionally, there is a thin layer of cells under the capsule, which is supplied by the capsular arteries. The posterior pituitary's entire blood supply comes from the inferior hypophyseal arteries. When the pituitary stalk is ruptured below the origin of the long portal veins as a result of head trauma, about 90% of the anterior lobe is infarcted, with only a few cells adjacent to the posterior lobe or the capsule of the gland surviving. However, the blood supply to the posterior lobe is not affected by stalk injury and the lobe does not become infarcted; rather, it is denervated (37).

In certain circumstances, rupture of the stalk may not necessarily be associated with infarction of the anterior pituitary. If the transection of the stalk passes above

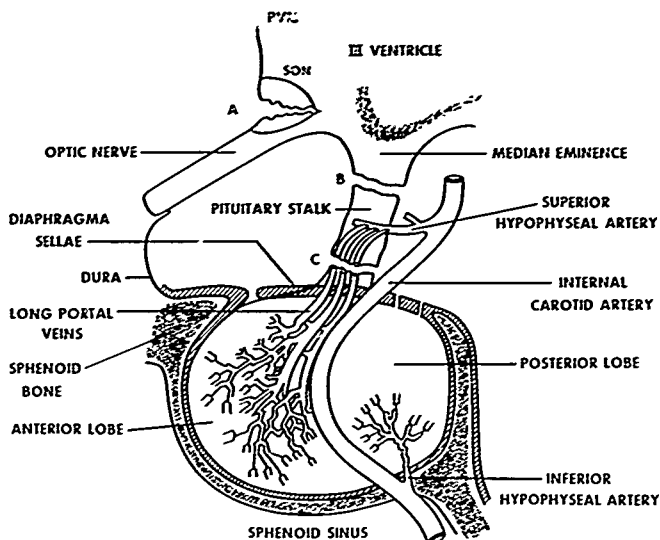


FIG. 1. Schematic presentation of anatomy and possible areas of damage to the hypothalamic-pituitary region. (A) The SON could be torn off or compressed when the brain makes a sudden movement because the dura tethers the optic nerve at the optic foramen. The PVN is less likely to be damaged, probably because it is farther away from the optic foramen. (B) High transection of the pituitary stalk may result in a rupture of the vessels to the hypothalamus, but portal vessels to the anterior pituitary may escape injury. (C) Low stalk transection may cause a rupture of the long portal vessels with a resultant massive infarction of the anterior pituitary. Lesions in the pituitary stalk will also interrupt the nerve fibers from the SON and PVN to the posterior pituitary.

the point of entry of the superior hypophyseal artery and the portal vessels are spared, then the anterior pituitary may not become infarcted (48). On the other hand, some studies show anterior pituitary infarctions with an intact stalk. These may result from shock or anoxemia following trauma, a state similar to Sheehan's postpartum infarction (97). Because the portal circulation is a low pressure end circulation, it is relatively vulnerable to shock. Furthermore, the pituitary gland is vulnerable to swelling, because the gland is confined within the sella turcica by the diaphragma sellae with a very small opening for passage of the pituitary stalk. When the gland swells as a result of cerebral edema, the fragile long hypophyseal vessels are usually compressed between the stalk and the free edge of the diaphragma sellae, resulting in anterior pituitary infarction (36,95,97).

The most common lesion in the posterior pituitary is acute hemorrhage. This is often petechial, but sometimes large enough to cause appreciable damage to the gland. Necrosis within the posterior pituitary itself is very rare (15).

FEATURES OF HYPOTHALAMIC-PITUITARY DEFECTS IN BRAIN TRAUMA

Hypothalamic Origin

Hypopituitarism may be caused by primary damage in the pituitary gland or it may be secondary to disorders in the hypothalamus. In many cases, clinical hypopituitarism and resultant hypothyroidism following head injury actually originated in the hypothalamus rather than the pituitary (29,31,60,86,122,154). In some cases, certain pituitary hormones [e.g., luteinizing hormone (LH) and follicle-stimulating hormone (FSH)] and target gland hormones (e.g., testosterone and estradiol) were low, but other hormones [e.g., thyroid-stimulating hormone (TSH) and prolactin (PRL)] were normal or even elevated (31,60,86,130,154). Responses of the pituitary hormones to exogenous thyrotropin-releasing hormone (TRH), gonadotropin-releasing hormone (GnRH), and lysine vasopressin (LVP) were preserved even during dexamethasone therapy, but they were delayed or blunted, indicating a hypothalamic defect and an inadequate pituitary "priming" (17,29,31,59,60,86,122,130,132,154,173). Since an intact hypothalamus is necessary for hypoglycemia to stimulate the anterior pituitary to secrete, no response to insulin-induced hypoglycemia was observed (7,86,105,132,151,154,167).

Less Frequent Anterior Pituitary Dysfunction

Anterior pituitary dysfunction following a traumatic brain injury has been reported infrequently despite a 22–45% prevalence of ischemic necrosis or hemorrhagic infarcts in the hypothalamic-pituitary region at autopsy (34,97). This discrepancy is due to several factors: (a) In terms of functional disruption, the anterior pituitary is less likely to be involved in cerebral injury than the posterior pituitary (86,153); (b) patients with severe anterior pituitary infarction may also have very severe brain injury and, therefore, they do not survive for the clinical appearance of anterior pituitary dysfunction (48,95); and (c) the pituitary gland has a very large reserve capacity. Two-thirds of the anterior pituitary must be destroyed before clinical signs of hypopituitarism develop and more than 90% must be destroyed before pituitary secretion totally ceases (95).

Less Frequent Involvement of ACTH

Anterior pituitary defects caused by injury may involve only one, several, or all of the tropic hormones. However, diminished adrenocorticotrophic hormone (ACTH) secretion is less common than that of the other pituitary hormones. The PVN, which contains the majority of corticotropin-releasing hormone (CRH)-containing neurons (68,83,146), is less commonly or less severely involved in the injury. Unlike the SON, direct tears in the PVN have not been observed (153). In addition, a secondary defect in ACTH secretion may not be present even if there is damage in the hypothalamus because the CRH-containing cells are present not only in the hypothalamus but also in many other locations. These include the basal telencephalon, brainstem, and much of the cerebral cortex (6,18,65,69,70), as well

as extraneural tissues (70). CRH cells have been found in the placenta (138), endocrine pancreas (120), and gastrointestinal tract (98). Though no conclusion as to the role of extrahypothalamic CRH in the regulation of ACTH has been reached, extrahypothalamic CRH may be released to stimulate the pituitary-adrenal axis (18). Finally, even if there is reduced ACTH secretion, there may not be an accompanying hypocorticalism, because many extrapituitary factors can stimulate the secretion of the adrenal cortex (127).

Early Recognition of Posterior Pituitary Dysfunction

Posterior pituitary dysfunction after head trauma is usually recognized during the early posttraumatic period either as frank diabetes insipidus (DI) or as a decreased ability to excrete free water (61). This is in contrast to traumatic anterior hypopituitarism, which is usually diagnosed long after the injury when clinical evidence of secondary end-organ failure has become evident (14,86,154).

MAJOR ENDOCRINE DISTURBANCES OCCURRING IN BRAIN TRAUMA

Hypothalamic-Pituitary-Adrenal Cortical (HPA) Axis

The HPA axis is a very important endocrine system because a sufficient circulating glucocorticoid level is necessary to maintain the sensitivity of vascular smooth muscle as well as the baroreceptor response to vasoactive agents (40). Recent studies suggest that brain receptors for mineralo- and glucocorticoids are involved in the central regulation of arterial blood pressure (156). Pathways mediating the ACTH response to general trauma have been well defined (16,76,94,95,125,170). Impulses initiated in the injured area traverse the peripheral nerves, and ascend through the spinal cord and brainstem to integrating centers in the reticular formation and limbic areas, where these impulses may or may not be modified by stimuli descending from the cerebral cortex. Impulses are then transmitted to the median eminence, where CRH is liberated. CRH enters the hypophyseal portal blood system, descends to the anterior pituitary cells, and interacts with highly specific receptors on the anterior pituitary cells to release ACTH. The ACTH is then transported via the systemic circulation to the adrenal gland, where it stimulates secretion of cortisol and aldosterone. Thus, when the brain is traumatized, ACTH secretion may be affected by exciting or inhibiting influences on the hypothalamus from stimulated cortical or subcortical areas; severed communications between the hypothalamus and other areas, or direct stimulation, inhibition, or destruction of hypothalamic or pituitary centers (42,94). These aberrations may be exhibited clinically in three ways: altered plasma hormone levels; changes in the relationship among the hormones derived from hypothalamus, pituitary, and adrenal glands, or a disturbed circadian rhythm (85).

Altered Plasma Hormone Levels

Clinical data show that brain trauma does not cause a high plasma ACTH level, or at least it does not increase the ACTH level as much as general trauma with a similar severity. In one study of 14 brain-injured comatose patients, the plasma ACTH level (45.6 ± 12.5 pg/ml) within 12–24 h of hospitalization was not signif-

icantly different from that obtained between 0900 and 1000 h in normal subjects (51.6 ± 3.8 pg/ml) (56). In another study, plasma ACTH levels within 2 h of injury were increased compared to normal controls, but were lower than those of trauma patients without major head injuries (median values of 96.8 vs. 201.6 pg/ml) (10). It has been reported that certain patients with pituitary stalk transection failed to respond to the metopirone test (103,128). This test examines pituitary corticotrophin reserve by producing inhibition of cortisol biosynthesis and thus stimulating ACTH secretion (152). The brain-injured patients with a limited response to metopirone had significantly longer comatose periods than those with normal metopirone test results (103,128).

An experimental study showed that the activation of neurons in the PVN by microinjection of L-glutamate, which is released in brain injury, elevated plasma levels of ACTH, arginine vasopressin (AVP), and oxytocin (41). However, global brain damage may not substantially increase ACTH secretion. Our study in rats showed that fluid percussion brain injury increased plasma levels in ACTH, corticosterone, and aldosterone 1 h after the injury, but the elevations in ACTH and corticosterone were not significant; only the aldosterone level exhibited a significant increase (179). Thus, brain trauma, like other types of trauma, usually stimulates the HPA axis, but if the hypophyseal portal veins are ruptured or the net neural influence on the hypothalamus is inhibitory, the response is reduced or absent and hypopituitarism may occur.

Plasma cortisol levels in brain trauma were found to be similar to those in general trauma (10,52,55,75,94,96,144). It appears that the more severe the brain trauma, the higher the plasma cortisol level (94). In critically ill patients, there is a shift in the steroidogenic pathways in favor of the production of cortisol (166) and this may also occur in brain trauma victims.

Changes in Relationship Among Hormones

Normally, adrenocortical secretion is controlled by ACTH, which is mainly governed by CRH. Elevated endogenous or exogenous glucocorticoid levels inhibit CRH and ACTH, and hence cortisol secretion (65,107,176). Current evidence suggests that cortisol may have no inhibitory effects at the pituitary level in vivo (54). However, these interactions can be modified under certain conditions (65,127). With moderate general trauma, both plasma ACTH and cortisol levels increased in proportion to the severity of the injury. However, at high severity scores, ACTH plateaued while cortisol decreased, indicating a poor response of the adrenal cortex to ACTH in severe trauma (10,145). In head trauma patients, the dissociation of ACTH and cortisol changes is in the opposite direction. Feibel et al. (56) showed that in head-injured patients the increased cortisol level was not accompanied by a correspondingly elevated ACTH level. Several possibilities may account for this discrepancy: the adrenal sensitivity to ACTH may be enhanced, peripheral metabolism of cortisol may be altered, extrapituitary sources of ACTH, including leukocytes, may modulate cortisol secretion during stress, or adrenocortical activation may be non-CRH or non-ACTH mediated (16,71,85).

Similar mechanisms may operate in other clinical settings. Vaughan et al. (157), studying 36 patients with severe burns, found very high cortisol levels but generally normal ACTH concentrations, with no correlation between the two. Other workers investigating acute hemorrhage also reported poor concordance between ACTH and corticosteroid levels (46,53,66,171,172).

In brain trauma patients, unusual factors may exist to strongly stimulate the HPA axis. It has been found that elevated intracranial pressure (ICP) is a potent stimulus for adrenocortical activation in the presence of normal brainstem function (56). Patients without intracranial hypertension had decreased plasma cortisol levels ($2.4 \pm 0.3 \mu\text{g/dl}$) within 36 h following head injuries. In contrast, those with intracranial hypertension had persistently elevated cortisol concentrations ($15.4 \pm 2.6 \mu\text{g/dl}$; $p < 0.001$), even though dexamethasone was given and the ACTH level was low ($22.4 \pm 10.1 \text{ pg/ml}$). When brainstem dysfunction was superimposed on the situation, the hypercortisolism disappeared and low cortisol levels occurred (56). It appears that normal brainstem function is necessary for adrenocortical activation in response to elevated ICP. At the present time, no specific locations within the brainstem can be precisely described as critical pathways for this effect.

It has been postulated that intracranial hypertension may alter the physiology of neuroendocrine systems by distorting the normal architecture of the hypothalamus or by producing ischemia in critical areas (34). Furthermore, an elevated ICP may remove normal hypothalamic or suprahypothalamic constraints on ACTH secretion, because there is evidence that the brain inhibits resting ACTH secretion (49,50).

Studies indicate that AVP plays an important role in mediating the intracranial hypertension-induced HPA response. CRH and AVP have been found in the PVN around the third ventricle (83), which is distorted when ICP is acutely elevated. There is a massive release of AVP in experimental intracranial hypertension. This enhanced release is not suppressed by hypotonic infusions (72). AVP has been shown both *in vivo* and *in vitro* to stimulate ACTH release directly from the anterior pituitary, and/or by way of CRH (19,20,67,73). It has also been claimed that AVP is the major dynamic mediator of ACTH secretion stimulated by α -adrenergic effects of catecholamines (3). Another study suggests that AVP may decrease ACTH production, but directly increase adrenal glucocorticoid production by activating baroreceptor reflexes (20). Regardless of the mechanism, AVP seems to be the most potent stimulus for overriding the normal suppression of cortisol secretion (20,142). Increased ICP, causing local disruption of normal hypothalamic anatomy to release AVP, may represent a unique type of stress to neuroendocrine systems, and thereby contribute to adrenal secretion by nonclassical pathways.

To our knowledge, no data are currently available to demonstrate changes in the relationships between CRH and subordinate hormones in head trauma.

Disturbed Circadian Rhythm

Loss of the diurnal rhythm of plasma ACTH and adrenocortical hormones has been observed after head injury (94). It has been reported that circadian rhythm

is preserved in patients undergoing laparotomy (104), but lost in about one-half of the head trauma patients (144). Disturbances in the circadian rhythm of ACTH and adrenocortical hormone secretions are thought to reflect early deficiencies in neuroendocrine control mechanisms (65).

Agrimonti et al. (2) examined the circadian profile of plasma cortisol and aldosterone in six patients who were comatose following trauma. Plasma cortisol and aldosterone levels were measured at 4-h intervals throughout three consecutive 24-h cycles in the first few days after trauma. A normally synchronized circadian pattern of plasma cortisol was recognizable in all cases. In contrast, no significant rhythm of plasma aldosterone was detected by cosinor analysis, and irregular fluctuations of this corticosteroid were recorded through the entire day. These data demonstrate that in the early posttraumatic period, comatose patients maintain a normal circadian rhythm of plasma cortisol and lose the rhythm of plasma aldosterone.

The pulsatile release of ACTH and cortisol may be in part the consequence of intrinsic rhythmic organization of the adenohypophyseal and adrenocortical cells (4,22). The isolated hamster adrenal gland in organ culture has shown rhythmic secretion of corticosterone for as long as 5 days in an environment devoid of ACTH (4). However, aldosterone secretion from the adrenal glomerular cells is affected by numerous stimulatory and inhibitory factors: plasma volume, plasma potassium, nutritional status, fluid infusion, administration of drugs, and so on (32). In addition, the aldosterone rhythm in normal individuals is markedly affected by the fact that they are in the upright position much of the day. The loss of normal mineralocorticoid rhythm following severe brain injury may reflect an alteration in these factors.

Pituitary-Thyroid Axis

General trauma frequently leads to low circulating triiodothyronine (T_3) and high reverse T_3 (rT_3) levels with TSH levels that are within the normal range or elevated (27,29,181). A recent study showed surgical trauma lowered the serum TSH level. This suppression lasted for only 1 day for the TSH morning value, but for 5 days for the TSH nocturnal surge (9). It has been demonstrated that rT_3 adversely affects while T_3 or TSH improves outcome after hemorrhage (139,178). In head-injured patients, the low T_3 and reciprocally high rT_3 seem to be similar to general trauma patients, but head trauma patients have significantly lower TSH plasma levels than patients with noncranial injuries. Furthermore, the more severe the brain injuries are, the lower the TSH and T_3 levels (28,29,60,122,130,175). Consistent with these clinical reports are animal studies, which showed that hypothalamic damage brought on deranged TSH regulation and thyroid dysfunction (30,148). In rats, damage to the PVN blunted the increase in plasma TSH in response to hypothyroidism (148). In dog and rabbit, hypothalamic compressive lesion led to a hypothyroidism within 4 weeks (30).

The relationship between responses to head trauma of thyroid and other neuroendocrine systems has been studied. Ziegler et al. (181) observed that severely injured (burned) patients had a strong negative correlation between norepineph-

rine and T_3 . This relationship became less remarkable in patients with injury to both brain and the other parts of the body, and completely lost in patients with severe head injury alone. This indicates that the inverse relationship between elevated norepinephrine and depressed T_3 levels in trauma patients is dependent upon an intact brain. Furthermore, Woolf et al. (175) found no correlation between thyroid hormone levels and the degree of adrenocortical secretion, implying that the thyroid hormone dysfunction in head trauma patients may be independent of a generalized stress response.

T_3 and thyroxine (T_4) have been reported to be within normal limits during the first 3 weeks following a severe traumatic brain injury (79). Plasma TSH and its response to TRH were also reported within the normal range when head trauma patients were admitted to the hospital (102,180). Thus, it seems that when the hypothalamus is injured, pituitary-thyroid function may be maintained for a relatively long period of time before a decline is apparent (102).

Pituitary-Gonadal Axis

Plasma LH levels in general surgical conditions may be elevated, but the timing of the response is variable. Aono et al. (5) observed a rise in LH during surgical procedures followed by a postoperative decline, whereas Charters et al. (27) reported no change during surgery and a decline postoperatively. Carstensen et al. (24) noted a postoperative elevation of LH that lasted for 1 week. FSH, in contrast to LH, is unlikely to increase during and after the surgery (5,27). However, the effects of GnRH on the secretion of FSH and LH may not be parallel, and FSH may have a GnRH-independent component to its secretion (80,133). Other studies of human gonadal hormone responses at the time of head injury show reductions instead of increases in blood levels. Rudman et al. (130) reported persistently decreased serum levels of FSH and LH in the early posttraumatic period in seven head-injured men. The decreases in both hormone levels corresponded to the degree and duration of coma. Woolf et al. (173,174) noticed that plasma levels of FSH, LH, testosterone, and estradiol fell in both men and women after brain injury, and that the magnitude of the hormonal dysfunction reflected the severity of the neurological deficit. Sequential observation showed a biphasic pattern in some patients. In one study, LH and FSH levels were elevated in three of six brain trauma patients during the first 28 h after injury, and then declined over the next 24 h (92). In addition, brain trauma can prematurely activate the hypothalamic-pituitary-gonadal axis in prepubescent individuals. This precocious puberty may result from damage to certain extrahypothalamic areas (e.g., limbic system), which have the ability to block off the normal inhibition of pituitary gonadotropin secretion (137).

GH

Elevation of serum growth hormone (GH) has been found during a variety of stressful states such as surgical procedures, trauma, and myocardial infarction (21,99,136). GH has also been found to be elevated in head trauma patients. King (92) showed that GH was initially increased in three of six patients and returned

to normal by the third to fifth day after head trauma. The increase was not related to the cerebral injury site or degree of trauma. On the other hand, head trauma may suppress GH secretion (51,147). In one study, an isolated GH deficiency and lack of GH response to growth hormone-releasing hormone (GRH) were reported 4 years after severe cerebral contusion and subdural hemorrhage (51).

Brain trauma may disturb metabolic control of GH secretion. Normally, glucose loading suppresses circulating GH in humans (65,123). In patients with head trauma, there is a paradoxical rise in serum GH in response to glucose (92). The phenomenon is temporary, however, with the normal suppressive response returning during recovery from the injury. A similar pattern of GH response to glucose administration has been described in patients with other cranial and systemic abnormalities, such as acromegaly (12), porphyria (119), hepatic cirrhosis (110), and neoplasia (13). These observations suggest that an increase in GH is a nonspecific indicator of hypothalamic dysfunction resulting from a variety of causes (35). Whether the paradoxical elevation is a result of increased GRH (somatotrinin) or decreased inhibiting factor [somatostatin, growth hormone-inhibiting hormone (SRIH)] or a disturbed inherent feedback relationship among GRH, SRIH, and CRH within the hypothalamus is unknown (106).

Prolactin

Head trauma usually causes an increase in PRL level over a period of time. Matsuura et al. (102) found increased serum PRL levels and lower PRL responses to TRH in 30 patients soon after head injury and before initial management. Valenta et al. (154) reported two patients who showed elevated serum PRL levels 6 to 12 months after severe head trauma. In another study of six patients with uncomplicated head trauma, three had elevated serum PRL levels (92). These reports are in agreement with an increased blood level described during general surgery and trauma (111), and also consistent with studies in rats, which showed that hemorrhage or immobilization stress increased plasma PRL levels (47,87). The increased serum PRL levels are related to the severity of the brain injury, indicating an impairment of prolactin-inhibiting hormone (PIH).

There have also been reports showing unaltered or slightly lower levels of PRL in comatose patients several weeks after the injury (28,60,130). The discrepancies in PRL response to head trauma could be attributed to several factors: the severity of head injury and duration of coma, time of study (early or late postinjury), the drugs used (steroids, catecholamines, analgesics, and so on), and the time during the circadian cycle.

AVP Disturbances: Syndrome of Inappropriate ADH Secretion (SIADH) and DI

AVP has been known as one of the principal hormones involved in water homeostasis (74) and arterial pressure control in both normal and pathological situations (77,131). Brain trauma may cause either insufficient or excessive levels of circulating AVP. In most cases, brain trauma, especially when not very severe, stimulates the hypothalamic-neurohypophysis system to release excessive AVP, rather than suppressing it (78,91). In one study, three patients showed a high

plasma AVP level (5.0 ± 1.6 pg/ml) within 2 weeks after head trauma, despite a plasma osmolality of less than 270 mOsm/kg. An osmolality this low would suppress plasma AVP to undetectable levels in normal humans (84). Chang et al. (26) measured the sequential changes of AVP content in the posterior pituitary and plasma AVP level in rats who sustained head trauma produced by dropping a weight. The AVP content of the posterior pituitary gland increased slightly 5 min after head injury, and then decreased gradually. The lowest value was 584 mU/gland (66 mU lower than the control value) at the end of the second day after head injury. The AVP content of the pituitary gland began to increase on the third postinjury day and returned almost to the control level by the 14th day. However, the change in plasma AVP level after head injury was different from that of the AVP content of the pituitary gland. Five minutes following head injury, the plasma AVP level increased more than fourfold from the control value (6 to 26 μ U/ml). This marked elevation in the plasma AVP level continued for 1 h following the head injury. The level then gradually decreased with time, but was still 10 μ U/ml higher than control values on the third day. When the posterior pituitary showed the least amount of AVP on the second day following the head injury, the plasma level was 14 μ U/ml, or twice the control value. On the 14th day after head injury, the plasma AVP level returned to normal. This study indicates that head injury immediately causes the pituitary gland to release AVP, and results in a high AVP level in circulation.

Prolonged and excessive secretion of AVP results in SIADH, which is characterized by a serum sodium less than 135 mEq/L, a serum osmolality less than 280 mOsm/kg, a sustained urinary osmolality greater than the serum osmolality, an absence of clinical evidence of volume depletion and heart or liver failure, and normal thyroid, adrenal, and renal function (88,140,155,158). This syndrome has been documented in severe head injury and following intracranial surgery, with an incidence of 0.8–30% (61,158). AVP increases the water content of normal and pathological brain tissue, and facilitates cerebral edema formation (44,62). Because this increased water content contributes significantly to an elevated ICP and cerebral circulatory and metabolic perturbations, early recognition is imperative (1,62).

Knowledge about AVP secretion under various pathological conditions has been accumulating for some time. The primary stimulus for AVP release is plasma osmotic pressure. When osmotic pressure is decreased, AVP secretion is inhibited within minutes (82,108,150,161,162). Many other nonosmolar factors also influence AVP release. The most common clinical situation is hypovolemia or volume redistribution (84). Baroreceptor-mediated AVP release involves impulses transmitted from the brainstem to the hypothalamus. The effects of these impulses are predominantly inhibitory. Any of a variety of lesions that interfere with any portion of the pathway to the hypothalamus may cause a decrease in the inhibitory input to the neurohypophysis and a subsequent increased release of AVP (74,129). There is a close inverse relationship between the rate of AVP secretion and the rate of discharge in afferents from the low- and high-pressure receptors in the vascular system. The low-pressure receptors monitor the fullness of the vascular system, and are the primary mediators of volume effects on AVP secretion (129).

Moderate decreases in extracellular fluid volume or in cardiopulmonary vascular fullness can increase AVP secretion without causing any change in arterial blood pressure (81,149). However, when the volume changes are large enough to produce a decrease in blood pressure, the carotid and aortic receptors play a greater role. It has been shown that the sensitivity of the low-pressure system is less than that for osmolality (164). However, once the volume is reduced below a threshold, release of AVP increases exponentially and finally reaches a level much higher than that achieved by osmolar stimulation (129). Hemorrhage releases a much greater amount of AVP than plasma hyperosmolality, and hypovolemia or sufficient reduction in the fullness of central circulation increases AVP secretion even if the plasma is hypotonic (129,149). Angiotensin II may reinforce and enkephalins may attenuate the AVP release in response to osmotic change (101,165). A variety of stimuli in addition to osmotic pressure changes and extracellular fluid volume aberrations also increase AVP secretion (90,129,160,163). The plasma osmotic pressure and other AVP-stimulating factors may not act in parallel. Therefore, the increased secretion of AVP in many instances could be related to and appropriate for these other stimulating factors.

The pathophysiology of hypersecretion of AVP begins with water retention, eventually leading to hemodilution. However, expansion of extracellular fluid volume causes an increased glomerular filtration rate, suppression of renin and aldosterone, and stimulation of ANP release. All of these can lead to a secondary natriuresis contributing to hyponatremia and hypo-osmolality (26,88,109,116,129). It has been reported that the signs of hyponatremia after head injury are alleviated following the administration of mineralocorticoids (84).

A reduced release of AVP and the resultant excessive loss of free water in the urine causes the syndrome of DI. This syndrome is characterized by hypernatremia, hyperosmolality, polyuria, and hyponatruia (88). Since the neurological condition of the patient can be adversely affected by the development of hypertonic coma, early recognition and correction are mandatory. Barreca and co-workers (8) performed endocrinological studies on 10 patients with posttraumatic DI and found that 8 of these patients had deficiencies of one or more anterior pituitary hormones. Therefore, the presence of DI calls for an early examination of anterior pituitary function (8,95,129).

Edwards and Clark (48) reviewed 53 severe brain trauma cases; DI occurred in 23 (43%). Barzilay and Somekh reported an incidence of 6.3% in 300 severely brain damaged children (11). However, among general hospital admissions, the incidence of DI was estimated to be 1:100,000, with a traumatic etiology in 2-16% of these (91). Thus, traumatic DI should be considered a relatively rare clinical event, arising only when there is severe brain trauma, and usually associated with a skull fracture and cranial nerve injury (91).

DI may be permanent or temporary. Permanent DI becomes apparent 1 day to 1 month later, because the intact posterior pituitary and lower stalk continue to release stored AVP with maintenance of water balance until AVP is exhausted (78). Head trauma patients with delayed onset of DI probably have a permanent AVP deficiency (78). Acute onset of DI following head trauma usually indicates a temporary AVP insufficiency (11). Temporary DI may be due to (a) inflammatory

edema in the hypothalamus or posterior pituitary with resolution as the swelling subsides, or (b) complete damage to the posterior pituitary with persisting symptoms until supraoptic and paraventricular neurons form new vascular connections (95).

Hyperglycemia and Hyperosmolar Nonketotic Coma

Hyperglycemia following brain injury has been described and regarded as the response to a severe hormonal disturbance (76,93). It includes true diabetes mellitus and nonketotic hyperglycemia.

Diabetes mellitus may occur in trauma patients when the enhanced secretion of cortisol, glucagon, catecholamines, and GH results in an impairment of insulin secretion and action (112). It has been demonstrated that β -endorphin acts centrally to cause hyperglycemia by stimulating sympathetic outflow and the pituitary-adrenal axis (124). The response of blood glucose to insulin in head trauma patients is frequently subnormal, particularly in patients with extremely high values of blood glucose (76). In one patient, a blood glucose level of 111 mmol/L showed no change following a total dose of 300 U of insulin (121).

Sequential changes in blood glucose and serum cortisol levels in brain-injured patients have been observed and correlated with the status of consciousness and outcome (118). In patients with brain injury, the changes in glucose and cortisol are directly related to the level of consciousness for 2 weeks postinjury; the deeper the coma, the higher the glucose and cortisol values. However, very higher blood glucose values are not associated with further elevations in cortisol levels, suggesting that other hormones such as glucagon, GH, and catecholamines may play a role in severe hyperglycemia (4,76). The severity and duration of the hyperglycemia has been used to predict the probability of survival following head injury (76,93,168). According to Pentelenyi and Kammerer (117), a fatal outcome is inevitable in brain-injured patients when blood glucose and cortisol levels consistently exceed 13 and 2200 nmol/L, respectively. These high levels of glucose and cortisol are not considered to be the causes of death, but the consequence of irreversible processes caused by severe brain damage (117). However, studies show that hyperglycemia decreases the tolerance of the brain to compromised cerebral blood flow and flow-metabolism uncoupling, both of which occur following traumatic brain injury (45,141,177).

In addition to the classic pituitary and hypothalamic hormones, other humoral factors have been found in the hypothalamus, and it has been claimed that they act directly on carbohydrate metabolism (76). The 13 amino acid polypeptide neurotensin has been isolated from hypothalamus and ileum. It has a dual role as a neurotransmitter and a gastrointestinal regulatory peptide (89). Neurotensin produces cyanosis, hypotension, increased secretion of LH and FSH, and a marked hyperglycemia (23). Another humoral factor has also been isolated from the ventrolateral hypothalamus and has been shown to stimulate isolated islets cells to secrete insulin (100).

In many individuals, the marked hyperglycemia after head injury bears little relation to true diabetes mellitus. A syndrome that satisfies the generally accepted

criteria of nonketotic hyperglycemia may be seen after severe head injury, cerebrovascular thrombosis, encephalitis, and heat stroke (65,121). This syndrome represents the clinical counterpart of a phenomenon that can be produced in animals by stimulation of the ventromedial hypothalamus (115, 143, 159) or intracerebroventricular administration of some neuropeptides, such as CRH and TRH (64).

The blood glucose level is controlled in the hypothalamus via both neural and humoral pathways in a manner similar to osmolality and core temperature (76,90,143). The immediate neural inhibition of insulin secretion and the direct activation of hepatic glucose release represent a rapid and efficient response to the urgent need for energy during stress (143). In addition, the neural influences are supplemented by hypothalamic control of the secretion of ACTH and GH from the pituitary and glucagon from the pancreas (143). There seem to be glucose-sensitive neurons in the hypothalamus, mainly in the ventromedial and lateral hypothalamus (113-115,135). These neurons monitor alterations in plasma glucose and make corresponding responses (90,135).

Loss of Body Temperature Control

Temperature changes have been observed in patients with cerebral trauma and intracranial hemorrhage; loss of body temperature control indicates clinical deterioration (30,134). Patients with signs of midbrain damage showed significantly reduced circadian rhythms of body core temperature. This suppression of rhythms was more marked in patients with acute brain injuries than with chronic damage (43). Fever of central origin was significantly associated with failure to recover consciousness. Survivors' body temperatures were significantly lower than nonsurvivors. Morphological examinations of nonsurviving patients confirmed that the lesions were mainly localized in the hypothalamic region and the extent of the damage was proportional to the severity of clinical signs.

Body temperature is primarily controlled by the hypothalamus (30,57). Animal studies have shown that pressor amines injected into the cerebral ventricles may cause an aberration in body temperature (33,58). In rabbits, some neurons lying within 2 mm of the midline of the anterior hypothalamus have shown a high degree of temperature sensitivity (135). Thermoregulatory disturbances may occur when the cavity or lining of the third ventricle is damaged or the hypothalamus is acutely compressed (30). It appears that body temperature is a highly sensitive parameter of hypothalamic function.

CONCLUSIONS

The pathological consequences of head injuries that affect the hypothalamus and pituitary have been well described, while only a limited number of cases of traumatic hypothalamic-pituitary dysfunction have been reported. An explanation for this disparity is that head injury of sufficient severity to cause hypothalamic or pituitary damage often leads to early death.

Patterns of endocrine abnormalities vary depending on the site of the injury. Injury predominantly to the hypothalamus can produce dissociated ACTH-

cortisol levels with little or no response to insulin-induced hypoglycemia and metopirone, hypothyroxinemia with a preserved TSH response to TRH, low basal gonadotropin levels with a normal response to GnRH stimulation, a variable GH level with a paradoxical rise in GH secretion after glucose loading, hyperprolactinemia, SIADH, temporary or permanent DI, disturbed glucose metabolism, and loss of body temperature control. Severe damage to the lower pituitary stalk or anterior lobe can cause low basal levels of all anterior pituitary hormones and eliminate responses to their releasing factors. Nevertheless, only a few cases have all the features of typical hypothalamic or pituitary dysfunction. In most cases, the injury is sufficient to damage both structures and produce a mixed endocrine picture. In addition, increased ICP, which releases AVP via changing normal hypothalamic anatomy, may represent a unique type of stress to neuroendocrine systems and may contribute to adrenal secretion by a mechanism that requires an intact brainstem.

With the improvement in rescue measures, an increasing number of severely head-injured patients with hypothalamic-pituitary dysfunction will survive to be seen by clinicians. Many of the clinical signs of hypopituitarism may have been incorrectly ascribed to postconcussion syndrome. Endocrine function should be investigated in brain-injured patients with basilar skull fractures and protracted posttraumatic amnesia, and patients with SIADH or DI should be checked for other endocrine abnormalities.

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